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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,315	08/10/2001	Charles S. Zuker	02307E-120110US	4699

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 01/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,315	ZUKER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-51 and 55-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-51 and 55-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/3/04 has been entered.

Applicant is notified that the amendments put forth on 11/3/04, have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Maintained Rejections:

Claims 49-51 and 55-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reason.

Claims 49-51 and 55-78 require a "functional effect", although the specification recites several examples of "functional effects" the skilled artisan could not be sure whether or not he or she was practicing the claimed invention because of the presence of such an ambiguous term.

Applicant argues that the examples provided in the specification provide sufficient detail to allow the metes and bounds of the claims to be determined. This argument has been fully

considered but not deemed persuasive. Examples can not define the bounds of a concept; and the claims are not limited to those examples, thus the bounds of the claims are subject to the interpretation of the individual and are thus indefinite.

Claims 49-51, 55-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying activators and inhibitors of sweet taste signal transduction, comprising a taste cell receptor composed of a heterodimer of SEQ ID NO: 9 and 15, wherein the receptor is present on the surface of a cell, and wherein the receptor is coupled to a Gα15 or Gα16 protein, does not reasonably provide enablement for methods employing artificially constructed variants of SEQ ID NO: 9 and 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) The claims encompass the use polypeptide variants of the polypeptides of SEQ ID NO: 9 and 15 (substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 9 or 15) i.e. protein variants encoded polynucleotides that need only hybridize to a polynucleotide encoding SEQ ID NO: 9 and 15. Although the specification indicates that such variants are encompassed by the invention (e.g. page 5), no specific teaching is provided to indicate which amino acid substitutions, deletions or insertions to make. The specification has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 9 or 15, but which still retain a desired property of the polypeptide of SEQ ID NO: 9 or 15. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein

corresponding to SEQ ID NO: 9 or 15 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the proteins corresponding to SEQ ID NO: 9 and 15 and variants of said proteins. If a variant of a protein corresponding to SEQ ID NO: 9 or 15 is to have a structure and function similar to a protein corresponding to SEQ ID NO: 9 or 15, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of a protein corresponding to SEQ ID NO: 9 or 15. Conversely, if a protein variant of SEQ ID NO: 9 or 15 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to

change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification provides the suggestion that such variants can be obtained, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those naturally occurring compositions known to the inventor, i.e. SEQ ID NO: 9 and 15. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). With regard to enablement for artificially constructed variants of the polypeptides of SEQ ID NO: 9 and 15, the instant fact pattern is actually one step removed and deficient from that of

Hyatt. The instant specification does not disclose any working examples of artificially constructed variants of the polypeptides encoded by SEQ ID NO: 9 and 15.

Applicant argues that given the advanced state of molecular biology an artisan could easily make a functional variant that is 90% identical to SEQ ID NO: 9 or 15 and that it is routine in the field to do so by avoiding areas of conservation between related sequences. This argument has been fully considered but not deemed persuasive. First, the claims are to a genus not to a single variant, such a genus not being supported by the specification. Regarding the advanced state of the art, Applicant is referred to Guo et al. PNAS 101(9205-9210)2004 wherein the authors completed a systematic study of the tolerance that natural proteins have to amino acid sequence change. They found that on average a single amino acid replacement had a 34% chance of inactivating a protein, see the Abstract. The instant SEQ ID NO: 9 and 15 are disclosed as consisting of 838 and 858 amino acids respectively. A polypeptide 90% identical to SEQ ID NO: 9 or 15 would have as many as 83 or 85 amino acid substitutions relative to SEQ ID NO: 9 and 15. Thus, the expectation that any given artificially synthesized polypeptide that is 90% identical to SEQ ID NO: 9 or 15 would be functional is astronomically low. Regarding Applicant's assertion that nondeleterious mutations could be made in areas that are not conserved among related members, Applicant is referred to Bowie et al. at page 1308, col 1, last paragraph. Bowie teaches "Functionally important residues should be conserved in sets of active sequences, bit it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding". No evidence has been put fourth to support Applicant's argument or refute the teachings of Bowie et al. referred to above and the analysis made in the

rejection. Arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

Applicant argues that an exhaustive teaching of all possible modifications of an exemplary T1R2 or T1R3 is a practical impossibility. This argument has been fully considered but not deemed persuasive. No such exhaustive listing has been required. Rather, the specification, which has failed to disclose even a single modification, has failed to provide an enabling disclosure for the claimed genus.

(B) The claims encompass methods of identifying sweet taste modulators wherein the receptor is not present in the membrane of the cell, e.g. claim 62 requires that the receptor be attached to a solid support. Thus, the receptor would somehow need to make an appropriate response to a ligand when the receptor was attached to a solid support. No specific guidance is provided as to what methods can be used to accomplish this. The art recognizes the difficulty in establishing functional responses of taste receptor G-protein coupled receptors. It does not appear to be routine in the art to produce functional responses from such receptors in anything other than the membrane of the cell, see page 382, col 1, middle paragraph of Lindemann, B. Nature Medicine 5(4)381-382, for example. In this regard the claims are also single means claims, because the claims encompass any method having the recited activities whereas the instant specification only discloses the single method known to the inventor.

Applicant refers to the Declaration of Dr. Zuker wherein Dr. Zuker asserts that there are many various methods for detecting sweet taste signal transduction in a cell-free context.

Applicant's arguments the Declaration of Dr. Zuker have been fully considered but not deemed persuasive and nor is the Declaration sufficient to overcome the rejection when weighed within the whole body of evidence on this issue. First it should be noted that Dr. Zuker is an inventor in the instant application, which can be considered as a factor in giving weight to the Declaration. Such ex parte affidavits must be closely scrutinized and weighed with care, it being kept in mind that they may unconsciously and unintentionally be colored as a result of enthusiasm for the subject matter of the application. An affidavit by an applicant or co-applicant as to the advantages of his invention is less persuasive than one made by a disinterested person. However, it is not to be disregarded for that reason alone and may be relied on when sufficiently convincing, see *Ex parte Coleman*, 29 USPQ 378, . *In re Mckenna et al.*, 97 USPQ 348, *Bullard &Co. v. Coe*, 64, USPQ 359. Second, it is difficult to determine whether or not Dr. Zuker's statements, referred to in Applicant's response, should be viewed as statements of fact, or of opinion, or of mere allegation. Affidavits or Declarations are provided as evidence and must set forth facts, not merely conclusions, *In re Pike et al.*, 84 USPQ235. Although in some cases it is appropriate to provide the reasoned opinion of an expert. In the instant case, Dr. Zuker is unquestionably an expert, but absent evidence to the contrary, his statements must be considered, at most, to be his opinions because there does not appear to be any evidence of the use, as claimed, of the polypeptides in a cell free context. Further, these opinions appear to be totally unsupported and uncorroborated, thus they cannot be considered reasoned opinions and are therefore simply allegations. The weight given to an affidavit or declaration depends on whether it presents allegations, opinions or facts. Generally facts are the most probative, opinions are less probative and mere allegations are not probative, see *In re Knowtton*, 183 USPQ 33, 37; *In re*

Brandstadter, 179 USPQ 286. The statements, referred to by Applicant, in the Declaration appear to occupy some sort of middle ground between opinion and allegation and cannot be given much weight.

One of skill in the art appreciates that many GPCRs have been assayed for activity attached to solid supports or other cell-free formats, however the instant GPCRs are highly atypical GPCRs and belong to a poorly understood family of GPCRs having extraordinarily large extracellular domains. Their functional characterization being much more problematic and not amendable to standard assays used with GPCRs in general, as exemplified by Lindemann, B. discussed above. Regarding the applicability of Lindemann, the Declaration asserts that while it is true that GPCR degradation, cell surface expression, and correct conformation are all potential problems that could complicate the functional analysis in a cell based-assay or even render such inoperable, this discussion does not stand for the position that a cell-free assay system cannot be used properly to assess the functional features of a G-protein coupled taste receptor. This argument has been fully considered but not deemed persuasive. The issue is not that the teachings of Lindemann preclude the eventual use of the proteins in a cell free functional assay, rather Lindemann teach the difficulty and lack of reasonable success the skilled artisan would expect to encounter while trying to do so. The instant specification has not provided specific teachings that would reverse that expectation.

Additionally, while ligand/receptor binding may be considered part of sweet signal transduction, there would be no expectation that simply measuring whether or not something stuck to the polypeptide in a cell free context would provide any useful information about whether or not the compound activated or inhibited the activity of the polypeptide.

(C) The specification puts forth that the sweet receptor can be coupled to a G-protein or a promiscuous Gα15 G-protein (see page12, line 23), however the only particular G-protein that is taught to work in the claimed invention is Gα15. The claims encompass, and the specification contemplates, using other G-proteins. The claims encompass the use of the endogenous G-protein(s) and the skilled artisan appreciates that such a use would be desirable, yet the specification has not provided any, and nor is such known in the prior art. Essentially, therefore, the specification has merely invited the skilled artisan to embark on an extensive research plan to try to find other G-proteins that would work in the invention. Such a call for extensive trial and error experimentation places an undue burden on the skilled artisan trying to practice the invention commensurate with the scope of what is being claimed. Additionally, in this regard the claims are also single means claims, because the claims encompass any method having the recited activities whereas the instant specification only discloses the single method known to the inventor.

Applicant argues that another promiscuous G-protein (Gα16) is known in the prior art. This argument is persuasive, and acknowledged above. However, the claims are not so limited. The Declaration and Applicant's arguments assert that gustducin "can be used in the present invention". This argument has been fully considered but not deemed persuasive. First, this statement does not appear to be supported in the instant specification. Second, it is unclear if the statement is a statement of fact that T1R3/T1R2 effectively couple to gustducin, as would be required to practice the claimed invention. It does not appear to be known in the art at the time of filing, or presently, what G-protein(s) couple to T1R3/T1R2.

Applicant's additional arguments regarding the use of taste cells expressing the endogenous G-proteins are not persuasive. The specification has not taught how to use such cells in the claimed methods. Further, as discussed above, there is no specific teaching as to how to measure receptor activation/inhibition in a cell-free system and particularly one wherein no G-protein is present.

Conclusion

This application contains claims 49-51, 55-78 which claim inventions nonelected with traverse. A complete reply to the final rejection must include cancelation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (571) 272-0829. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

January 19, 2005